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Serum sickness-like reaction following an administration of the first dose of inactivated COVID19 vaccine: a case report.

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Introduction

Numerous vaccine-related adverse reactions emerge amidst an emergency rollout of COVID-19 vaccines. The nature and incidence of these reactions varies according to the type of vaccine. An inactivated COVID19 vaccine (CoronaVac: Sinovac, Beijing) is widely distributed in Thailand and several other countries. It has been considered relatively safe, with the most commonly encountered side effects being injection site reactions, fever, fatigue, diarrhea, and muscle pain[1]. Regarding cutaneous side effects, discoloration at the injection site and pruritus have been reported from vaccine trials.[1] Herein, we present a case of a severe adverse reaction to the inactivated COVID19 vaccine. The patient developed serum sickness-like reactions four days after receiving the first dose of the vaccine, which required a prolonged course of systemic corticosteroid and precluded the patient from receiving further doses of the vaccine. This condition occurs rarely in association with vaccination; previous cases were found only in case reports and small observational studies[2-4].

Case report

A 43-year-old previously healthy female patient presented to a dermatology outpatient clinic with pruritic blanchable erythematous macules and patches and excoriated papules and plaques on her trunk and extremities, which resolved with post-inflammatory hyperpigmentation (Figure 1: A-D). The lesions on the chest and right posterior shoulder exhibited a feature resembling reticulate

erythema (Figure 1B and 1D). Four days prior, the patient had received the first dose of an inactivated COVID19 vaccine (CoronaVac; Sinovac, Beijing) without immediate adverse reaction. The rashes started as a single patch on the chest and became generalized within nine days; they appeared randomly and did not follow a pattern of centrifugal distribution. The rashes were accompanied by fever (body temperature: 38.1°C), generalized malaise, severe myalgia and arthralgia, and cervical lymphadenopathy. Before this presentation, the patient had not had any recent history of respiratory tract infection, taken any medication, vaccination, or blood transfusions. Laboratory investigations revealed leukocytosis predominated by neutrophils and elevation of various inflammatory markers, including erythrocyte sedimentation rate (ESR) (42 mm/hr, normal range: 4-20), C-reactive protein (165.74 mg/L, normal range: 0-5), ferritin (3210.2 ng/mL, normal range: 15-150), and lactate dehydrogenase (336 U/L, normal range: 125-220). Chest X-ray, urinalysis, and serum creatinine level were normal. Serology for hepatitis viruses indicated an inactive carrier state for hepatitis B virus infection (viral load 24 IU/mL with normal liver function tests) and the absence for hepatitis C infection. Hemocultures, nasopharyngeal swabs for SARS-CoV-2 RT-PCR, antinuclear antibodies, and rheumatoid factors were negative. Complement levels, including C3c and C4, were normal. Anti-CIC C1q IgG, which indicates the presence of an abnormal circulating immune complex, was also negative. Biopsy of the lesional skin demonstrated superficial perivascular and interstitial inflammatory cell infiltrates (Figure 2) composed of lymphocytes, neutrophils, nuclear dust, and extravasation of erythrocytes (Figure 2: inset). Fibrinoid necrosis of the blood vessel wall was not observed. Histopathological differential diagnoses might encompass urticarial vasculitis; nonetheless, the overall clinical presentation, the temporal relationship with the vaccine, together with the normal complement levels, favored the diagnosis of vaccine-related serum sickness-like reaction (Table 1). The diagnosis prompted the

prescription of high-dose oral corticosteroid treatment (prednisolone 1 mg/kg/day), colchicine (1.2 mg/day), antihistamines, and a moderate-potency topical steroid. Given the rapid improvement of the patient's condition in less than a week, a 2-week taper was attempted; however, the symptoms recurred with this regimen. Therefore, prednisolone was reintroduced at 15 mg/day with gradual tapering guided by ESR levels. After two months of treatment, inflammatory markers normalized, allowing a slow withdrawal of corticosteroid treatment while continuing others. Because of the prolonged course and severity of the illness, the caring physicians and the patient agreed to cancel further vaccine doses. The reaction was reported to the vaccine adverse event reporting system.

Table 1. Clinical features of SSLR and its main differential diagnoses

	SSLR[5, 6]	**Serum sickness syndrome**[5, 6]	**Urticarial vasculitis**[7]
Patient characteristics	children > adult, no sex predilection	no age or sex predilection	adult > children, women > men
Causes	- Most common: medications (cefaclor, penicillins, minocycline, NSAIDs, bupropion, propranolol, sulfonamides, phenytoin) - Others: biologics, vaccines	- Most common: venom or microbial antitoxins - Others: anti-thymocyte globulin, biologics, vaccines	- Most common: idiopathic - Others: medications, infections, autoimmune diseases, myelodysplastic disorders, malignancies
Disease onset after the exposure	5-10 days	1-2 weeks	Variable
Skin manifestations	- Pruritic blanchable urticarial plaques or morbilliform eruption on the trunk and extremities	- Pruritic blanchable urticarial plaques, morbilliform eruptions, or palpable purpura on the trunk and extremities; often start around the drug injection site and becomes most prominent at the lateral side of the junction between palmoplantar and dorsum sides of hands and feet.	- Nonpainful or partially blanchable indurated wheals (0.5-5 cm) with a central dark-red or brown area, lasting for several days and leaving residual hyperpigmentation. - True urticarial and angioedema occur in 50% of patients.
Systemic manifestations	Fever, arthralgia, abdominal pain, lymphadenopathy	Common: fever, malaise, arthralgia or arthritis Uncommon: facial or peripheral edema, lymphadenopathy, splenomegaly, glomerulonephritis, gastrointestinal symptoms or intestinal ischemia, uveitis, peripheral neuropathy	Common: fever, arthralgia or arthritis, myalgia Uncommon: glomerulonephritis, chronic obstructive lung disease or pleuritis, gastrointestinal symptoms or intestinal ischemia, ocular inflammation (uveitis, episcleritis, conjunctivitis)[a]
Circulating immune complexes	No	Yes	Yes
Laboratory findings[b]	- Normal serum complement levels - Absence of anti-C1q antibodies	- Low serum complement levels - Elevated anti-C1q antibodies	- Low or normal serum complement levels[a] - Elevated anti-C1q antibodies observed in 50-100% of patients
Histopathology	- Perivascular and interstitial mixed cell infiltrates; no or scant vasculitis.[8] - DIF: negative	- Leukocytoclastic vasculitis - DIF: Deposits of immunoglobulins and complements within vessel walls	- Leukocytoclastic vasculitis - DIF: Deposits of immunoglobulins and complements within vessel walls
Clinical courses and prognosis	- Self-limiting after the removal of causative agents - No long term sequalae - May require NSAIDs, antihistamines, and systemic corticosteroids for symptom control.	- Spontaneously improve after the withdrawal of causative agents - Prognosis depends on the degree of systemic involvement - NSAIDs, antihistamines, systemic corticosteroids, and plasmapheresis are warranted in severe cases.	- Mostly chronic (resolved in only 30-40% of patients in one year) or recurrent (4-8 weeks per episode). - Requires immunosuppressive therapy for disease control.

a Hypocomplementemic urticarial vasculitis is more common than the normocomplementemic variant; serum complement levels and anti-C1q antibodies are inversely proportionate to the extent and magnitude of systemic involvement. Systemic involvement is rare in the case of normocomplementaemic urticarial vasculitis. b Non-specific elevation inflammatory markers can be observed in patients with SSLR, serum sickness syndrome, and urticarial vasculitis.

Abbreviations: NSAIDs: nonsteroidal anti-inflammatory drugs, SSLR: serum sickness-like reaction

Discussion

Serum sickness syndrome (SS) is an immune-complex mediated hypersensitivity reaction that occurs following vaccination and protein-based medications.[6] By contrast, serum sickness-like reaction (SSLR), despite its clinical resemblance to SS, currently have unclear pathogenesis although current evidence suggests that it is not mediated by abnormal immune complex formation.[5] This delayed hypersensitivity reaction was first described as a drug-induced reaction and is rarely encountered in adults; it is more frequently found in children with an incidence of approximately 7%.[5] Its clinical manifestations are remarkably similar to those of SS and include fever, malaise, arthritis or arthralgia, and rashes.[5, 6] The rashes observed in SSLR are non-specific and may include urticaria, morbilliform eruption, and polycyclic plaques.[5] Histopathology of the rashes usually reveals the features of neutrophilic urticaria without vasculitis.[8, 9]

The differential diagnoses of SSLR include SS, normocomplementaemic urticarial vasculitis, viral exanthem, Adult Still's disease, and Schnitzler's syndrome. Among these diagnoses, SS and urticarial vasculitis can be challenging to differentiate from SSLR, as the diagnosis is based on clinical grounds (Table 1). Though extravasation of erythrocytes observed in our case may raise suspicion for urticarial vasculitis, scant perivascular leukocytoclasis has been reported in a previous case of SSLR[8], and therefore, is not necessarily indicate the presence of vasculitis. Additionally, joint involvement is mainly found in hypocomplementaemic urticarial vasculitis rather than in normocomplementaemic urticarial vasculitis.[7] Besides, although not all viral infections are investigated, these diagnoses are unlikely as they are usually accompanied by other features characteristic to the specific viral infections (e.g., transaminitis for viral hepatitis, pharyngitis for EBV infection).

To date, causes of SSLR reported in adults include antibiotics, psychiatric drugs (mostly bupropion), biologics, and vaccines. Influenza[4], hepatitis B[3], and rabies[2] vaccines were reported as causes of SSLRs. Our case adds inactivated COVID19 vaccine to the list of disease triggers, even though previous unreported SSLR cases related to this vaccine may be grouped under an umbrella term of hypersensitivity reactions.[1] Recognition of this condition is crucial since it precludes the patients from receiving further doses of the vaccine, unless there is an absolute necessity that outweighs the risk of re-developing this condition. Successful attempts of desensitization in patients who developed SSLR have been documented in only a few cases.[10]

Regarding disease prognosis, SSLR is self-limited within 1-2 weeks upon removing the causes.[6] However, nonsteroidal anti-inflammatory agents or corticosteroid treatment may be needed for patients with severe disease.

Abbreviations used:

COVID-19: coronavirus disease 2019

ESR: erythrocyte sedimentation rate

HBV: Hepatitis B virus

NSAIDs: nonsteroidal anti-inflammatory drugs

SSLR: serum sickness-like reaction

RT-PCR: reverse transcription polymerase chain reaction

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Figures (Color should be used for both figures in print)

Figure 1. Cutaneous findings Erythematous patches with excoriation on the trunk and extremities with post-inflammatory hyperpigmentation **(A-D).** Some lesions show a feature resembling reticulate erythema **(B, D)**.

Figure 2. Histopathology of the skin lesion superficial perivascular and interstitial inflammatory cell infiltrates (original magnification, ×100). **Inset** The inflammatory cell infiltrates composed of lymphocytes, neutrophils, nuclear dust, and extravasation of erythrocytes (original magnification, ×400).